Exhibit B

10761 King William Drive | Dallas, TX 75220
Phone: 469-484-1927 | Fax: 469-484-1930 | www.USPlabsDirect.com

Contains Trade Secrets and
Confidential Commercial Information
Not For Public Disclosure

May 15, 2012

Quyen Tien
Division of Enforcement
Office of Compliance (HFS-608)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740-3835

Re: Warning Letter No. 285519 (April 24, 2012)

Dear Mr. Tien:

This letter responds to the warning letter from Michael W. Roosevelt (the Roosevelt letter) dated April 24, 2012, regarding the marketing of our dietary supplements that contain the dietary ingredient, 1,3-dimethylamylamine HCl (DMAA). The Roosevelt letter states that (1) FDA knows of no information demonstrating that DMAA is a dietary ingredient, (2) assuming DMAA is a dietary ingredient, it is a new dietary ingredient (NDI) for which a notification has not been submitted, and (3) FDA knows of no evidence demonstrating the safety of DMAA as a dietary ingredient. This letter and its appendices demonstrate that DMAA complies with the applicable requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for a lawful dietary ingredient and does not present a significant or unreasonable risk of illness or injury to consumers under the conditions of use recommended or suggested in the labeling.

I. DMAA is a Dietary Ingredient

The intent of Congress to authorize the marketing of a wide range of dietary ingredients is evident in its broad and comprehensive definitions of a "dietary supplement" and a "dietary ingredient." Section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a dietary supplement as:

> a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract or combination of any ingredient described in clause (A), (B), (C), (D), or (E).[1]

The dietary substance involved here, DMAA, satisfies the statutory definition of a dietary ingredient in two ways: (1) under Sections 201(ff)(1)(C) and (F), as a constituent of a botanical -- the geranium plant -- and (2) under Section 201(ff)(1)(E), as a dietary substance for use to supplement the diet.

A. Geranium is a Botanical

The FD&C Act does not define the word "botanical." According to the *Concise Oxford English Dictionary*, the word "botanical" means "a substance obtained from a plant and used as an additive."[2] Geranium (*Pelargonium graveolens*), as described in *The Oxford Companion to Food*, is a popular garden plant, i.e., a botanical.[3] DMAA is a substance obtained

---

[1] FD&C Act § 201(ff)(1).

[2] Concise Oxford English Dictionary 162 10th ed. (2002) (Appendix 1).

[3] Alan Davidson, The Oxford Companion to Food 336 (Tom Jaine ed., 2d ed. 2006) (Appendix 2).

from the geranium plant. It is found in the oil obtained from the steam distillation of or extraction from geranium stems and leaves and is used as an additive.

B. DMAA is a Constituent of Geranium

Three independent scientific studies have verified the presence of DMAA as a constituent in geranium stems and leaves.

1. The Ping Study

The first of these studies was conducted by Ping et al., and was published in the *Journal of Guizhou Institute of Technology* in 1996.[4] The Ping study performed capillary gas/chromatography-mass spectrometry analysis of geranium oil, which they obtained after they procured fresh air-dried stems and leaves from the Rongjiang region of the Guizhou province in China. The report of the Ping study identified DMAA as a constituent of the geranium plant grown in that region.

Critics of the Ping study erroneously cite published papers reporting studies that fail to find DMAA in geranium oil. The primary limitations of these studies are that (1) they were designed to detect major constituents of geranium, but not constituents that appear in small amounts (none of these studies accounted for all constituents of the geranium they analyzed), (2) the analytical methods they used were not well suited for detecting DMAA in a complex matrix like geranium oil that contains hundreds of constituents, and (3) they did not use geranium oil from the Rongjian region of the Guizhou province in China, or from China at all, despite the fact that geranium oil from China is different from other types of geranium oil.

---

[4] Ping Z, Jun Q, and Qing L, *A Study on the Chemical Constituents of Geranium Oil, J. of Guizhou Institute of Technology*, volume 25, at 82-85 (February 1996) (the Ping Study) (Appendix 3). A copy of the article as published in Chinese is attached in Appendix 4.

2. The Intertek Study

Intertek Health Sciences International, a leading scientific consulting firm that specializes in food science, has conducted a laboratory analytical study that documents in detail the presence of DMAA in geranium.[5] In its assessment of the results of the Intertek study, Cantox definitively concluded that DMAA exists in geranium oil and geranium plant tissues.[6]

3. The Simone Study

A third study, by Dr. Paul Simone of the University of Memphis, to determine whether DMAA is present in the geranium plant has just been completed, and an abstract of the results of the study is now available.[7] The study first retested a sample that had been tested by Intertek, and confirmed that it contained DMAA. They then tested samples from three geographically different areas. One sample had detectable DMAA and two did not. Because the presence and level of DMAA in geranium varies in different geographical areas, this is not a surprising result.

As these three independent scientific studies show, DMAA is a constituent of geranium, which makes DMAA a dietary ingredient under Section 201(ff)(1)(C) and (F).

---

[5] Intertek Health Sciences International, *DMAA: Review of Safety Data and Occurrence in the Geranium Plan and Its Essential Oil* (February 6, 2012) (Appendix 5); Barry Lynch, *Memorandum* (September 6, 2011) (Appendix 6)

[6] Intertek Health Sciences International, *supra* n. 5, at 13.

[7] Fleming HL, Ranaivo PL, and Simone PS, *Analysis of 1,3- and 1-4 Dimethylpentylamine in Geranium Herb by LC-MS/MS* (Abstract) (May 2012) (Appendix 7).

C. DMAA is a Dietary Substance for Use to Supplement the Diet

DMAA is a dietary ingredient under Section 201(ff)(1)(E) because it is a "dietary substance for use by man to supplement the diet by increasing the total dietary intake." DMAA, as part of the geranium plant, has been consumed as a dietary substance for over a century.[8] Geranium leaves are infused for use as a tea and are added to desserts and confections.[9] DMAA has been consumed in geranium oil that is used as a flavoring agent.[10] Even FDA has recognized the use of geranium ingredients in food by classifying geranium as generally recognized as safe (GRAS) for use in food.[11] And DMAA is marketed specifically to increase the dietary intake of DMAA, the necessary prerequisite to qualifying as a dietary ingredient under Section 201(ff)(1)(E). As such, DMAA qualifies as a dietary ingredient under Section 201(ff)(1)(E), in addition to qualifying as a dietary ingredient under Section 201(ff)(1) (C) and (F).

II. Both Natural and Synthetic DMAA Qualify as a Dietary Ingredient

The Roosevelt letter states that synthetic DMAA is not a dietary ingredient. As explained below, the position taken in the Roosevelt letter that a synthetic ingredient that is chemically identical to a dietary ingredient found in nature cannot be a dietary ingredient is contrary to the statutory language and the intent of Congress in enacting the Dietary Supplement Health and Education Act (DSHEA).

---

[8] The Oxford Companion to Food, *supra* n. 3, at 336.

[9] Deni Brown, Encyclopedia of Herbs & Their Uses 324 (1995) (Appendix 8).

[10] The Oxford Companion to Food, *supra* n. 3, at 336.

[11] 21 C.F.R. §§ 182.10 and 182.20.

Synthetic ingredients that are chemically identical to naturally derived ingredients, such as DMAA, may be marketed under both Sections 201(ff)(1)(C) and (F) and Section 201(ff)(1)(E) of the FD&C Act. No distinction is made in the statute between natural and synthetic dietary substances, and FDA has never previously established such a distinction. If such a distinction were to be established in the future, it must be made through notice-and-comment rulemaking under the Administrative Procedure Act,[12] not in a letter.

FDA has a long history of recognizing that synthetic ingredients identical to natural ingredients should be treated the same. FDA's nutrition labeling regulation states that a food is deemed misbranded if its labeling states or implies "That a natural vitamin in a food is superior to an added or synthetic vitamin."[13] This prohibition dates back to the late 1960s, when the agency vigorously defended its position on this issue during two years of public hearings on special dietary food regulations.[14] At the end of that formal rulemaking process, FDA concluded that "There is no nutritional difference between a vitamin provided by a synthetic source and the same vitamin provided by a natural source . . . ."[15]

As recently as the late 1990s, FDA reaffirmed the validity of the prohibition on distinguishing between natural and synthetic ingredients, stating that it is "aware of nothing that establishes that a claim of difference between the natural and synthetic version of the same form

[12] 5 U.S.C. § 553.

[13] 21 C.F.R. § 101.9(k)(4).

[14] These hearings took place between 1968 and 1970. *See* 38 Fed. Reg. 2143, 2147, 2150 (January 19, 1973).

[15] *Id.* at 2147.

of a nutrient is not misleading."[16] Denying the validity of synthetic botanical extracts would suggest that FDA now views a material distinction between synthetic and natural versions of identical ingredients. This radical shift makes no sense in light of the agency's consistent historical policy.

B. FDA Has Approved Both the Natural and the Synthetic Sources of Essential Vitamins

Several concrete examples illustrate that FDA recognizes the equivalence of naturally extracted sources and synthetic counterparts of dietary ingredients. FDA has affirmed as GRAS both natural and synthetic riboflavin,[17] vitamin A,[18] and vitamin D.[19] FDA approved the food additive Vitamin D_3 in both natural and synthetic forms.[20] And FDA has acknowledged new dietary ingredient (NDI) notifications for nature-identical synthetic botanical ingredients without objection in the past. For example, in March 2001 FDA determined that "Roche synthetic zeaxanthin is identical to natural zeaxanthin."[21]

C. Distinguishing Between Natural and Synthetic Versions of Dietary Substances is Inconsistent with FDA Policy on Genetically Engineered Food

As evinced in the domain of genetically engineered food, FDA has long maintained that the method of a product's manufacture is not a material fact unless it renders a

[16] 62 Fed. Reg. 49826, 49841 (September 23, 1997).

[17] 21 C.F.R. § 184.1695(a).

[18] 21 C.F.R. § 184.1930(a).

[19] 21 C.F.R. § 184.1950(a).

[20] 21 C.F.R. § 172.380(a).

[21] Letter from A. Davidovich, Roche Vitamins, to Office of Nutritional Products, Labeling, and Dietary Supplements, CFSAN, submitting Rpt. 96, Docket No. FDA-1995-S-0039 (March 22, 2001).

substantive change in the product itself.[22] With regard to genetically engineered foods, FDA has repeatedly concluded that a genetically engineered food does not differ in any material respect from a traditional food. FDA has therefore concluded that it lacks the statutory authority to require any special labeling for genetically engineered food. The agency's position has been upheld in court.[23]

Here, synthetic DMAA is indistinguishable from naturally occurring DMAA. As discussed above, DSHEA draws no distinction between two chemically identical dietary ingredients. FDA's conclusion to the contrary is unsupported by the statutory text, is contrary to Congress's goal that consumers have access to a wide variety of dietary supplements, is contrary to the agency's position on genetically engineered foods, and is not grounded in any scientific or public health basis. Indeed, if FDA were to adopt the position espoused in the Roosevelt letter the agency would inherently reopen its longstanding policy on the approval and labeling of genetically engineered food.

---

[22] 57 Fed. Reg. 22984, 22991 (May 29, 1992). The agency reaffirmed this policy in developing its 2001 guidance on genetically engineered foods. FDA, *Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering* (January 2001) (stating that "The agency is still not aware of any data or other information that would form a basis for concluding that the fact that a food or its ingredients was produced using bioengineering is a material fact that must be disclosed under sections 403(a) and 201(n) of the act.").

[23] *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 178-78 (D.D.C 2000) (concluding that FDA's assertion that it lacks the statutory authority to require special labeling for genetically engineered foods was not arbitrary or capricious); *Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995) (holding that FDA did not act arbitrarily and capriciously in not requiring the labeling of dairy products derived from cows treated with bovine somatotropin).

D. FDA Has Determined that Synthetic Dietary Substances are Dietary Ingredients

The breadth of Section 201(ff)(1)(E) demonstrates Congress's goal of securing consumer access to a wide variety of safe and beneficial dietary supplements and dietary ingredients.[24] The only prerequisite to being considered a dietary ingredient under Section 201(ff)(1)(E) is that the dietary ingredient be used to supplement the diet.

FDA has previously acknowledged the breadth of Section 201(ff)(1)(E) in the preamble to its regulation on requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements.[25] There, the agency stated in a Federal Register preamble -- which constitutes a formal agency advisory opinion[26] -- that a substance such as CoQ10 -- which is commonly synthesized -- falls within the broad range of dietary ingredients that Congress contemplated.[27] FDA's acceptance of a broad range of dietary ingredients is consistent with the fact that neither the language of DSHEA nor its legislative history reveals any congressional intent to exclude synthetic versions of natural botanical extracts from the definition of a "dietary ingredient."

---

[24] "Legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness." DSHEA, Pub. L. No. 103-417, § 2(15)(A), 108 Stat. 4325, 4326 (1994).

[25] 62 Fed. Reg. 49859, 49860 (September 23, 1997).

[26] 21 C.F.R. 10.85(d)(1).

[27] *Id.* (quoting from the legislative history of "other nutritional substances" -- a precursor to "dietary ingredients" -- statements that numerous ingredients not traditionally or historically viewed as food substances would be included, such as primrose oil, black currant seed oil, amino acids, and hydrogen peroxide).

E. Common Use in Food is not a Statutory Requirement for a Dietary Ingredient

The Roosevelt letter suggests that synthetic DMAA may not be considered a dietary ingredient under Section 201(ff)(1)(E) because synthetic DMAA has not been commonly used as a food or drink. But neither the text of Section 201(ff)(1)(E) nor any legislative history contains or implies any such historical-use requirement. Section 201(ff)(1)(E) requires only one prerequisite for a dietary ingredient: that the dietary ingredient be used to supplement the diet. Where Congress intended to impose a historical-use requirement in DSHEA, it did so expressly.[28] The absence of a historical-use requirement in Section 201(ff)(1)(E) makes clear that Congress intended to apply no such limitation on the dietary ingredients encompassed by Subparagraph (E). Section 201(ff)(1)(E) contains only a forward-looking assessment. FDA's attempt to read a historical-use requirement into Subparagraph (E) is contrary to a fundamental canon of statutory construction: "*expressio unius est exclusio alterius*" (the inclusion of one is the exclusion of others). Finally, even if such a requirement had been included in the statute, the use of geranium in the food supply for more than a hundred years would satisfy it.[29]

F. Distinguishing Between Natural Dietary Substances and their Synthetic Counterparts Represents Detrimental Public Policy

As a practical matter, if FDA's interpretation of Section 201(ff)(1)(E) were correct, and synthetic botanicals were disqualified from being "dietary ingredients" altogether, such an interpretation would have a serious unintended public consequences. Manufacturers typically have more control over synthetic processes than over natural extraction processes, and

[28] *E.g.*, FD&C Act §§ 413(a)(1), (d).

[29] See Part I(C) of this letter.

this control can yield tangible safety and quality benefits for consumers. Synthetic processing can eliminate potentially harmful variables such as pesticide contamination, the presence of foreign materials, and the uptake of heavy metals and toxins from the soil. Chemical synthesis also ensures greater consistency in output quality, as variations in climate or geographic region no longer pose concerns.

Discouraging the industry's use of synthetic processing can also negatively affect the environment. If a chemical component of a plant has beneficial health effects, but turns out to be difficult to extract from its natural source on a commercial scale, the position taken in the Roosevelt letter would force industry to destroy botanicals on a large scale in order to obtain a commercial supply. The result would be to require a manufacturer to produce it in an unsustainable or environmentally irresponsible manner.[30] This simply is not what Congress intended.

III. Because DMAA Is Found In Food, No NDI Notification Is Required

The Roosevelt letter asserts that, even if DMAA is a "dietary ingredient" -- which, for the reasons explained above, it is -- DMAA must be the subject of an NDI notification

---

[30] The detrimental impact that the agency's policy would have on the environment has been demonstrated previously with regard to taxol, which is derived from the bark of the Pacific yew tree. The production of small amounts of natural taxol required use of large numbers of Pacific yews. Congress became concerned with the detrimental effect that the development of taxol had on the Pacific yew and therefore passed the Pacific Yew Act. Pub. L. 102-335, 106 Stat. 859 (1992). In the Act, Congress specifically stated that "appropriate management guidelines must be implemented promptly in order to prevent any wasting of the Pacific yew . . . while successful and affordable alternative methods of manufacturing taxol are being developed." By the end of 1994, Bristol-Myers Squibb discontinued selling taxol derived from the Pacific yew, and began selling only taxol that was developed through a semisynthetic alternative method of manufacture. *New Version of Taxol is Approved by F.D.A.*, N.Y. Times, December 13, 1994, *available at* http://www.nytimes.com/1994/12/13/science/new-version-of-taxol-is-approved-by-fda.html.

Section 413(d) of the FD&C Act defines an NDI as a dietary ingredient that was not marketed in the United States before October 15, 1994, and which does not include any dietary ingredient that was marketed in the United States before that date.[31] Under Section 413(a), a dietary supplement containing an NDI will be deemed adulterated unless it meets one of the following two requirements: (1) it contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered, or (2) notification is submitted to FDA by the manufacturer or distributor of the dietary ingredient or dietary supplement that there is a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions of use recommended or suggested in its labeling, will reasonably be expected to be safe.[32] An NDI that satisfies Section 413(a)(1) is exempt from the NDI notification requirement found in Section 413(a)(2).

Under Section 413(d), DMAA is an NDI because it was not marketed in the United States prior to October 15, 1994. But as explained in Part I(C) of this letter, DMAA has been present in the international food supply for over a century in a variety of ways and synthetic DMAA is chemically identical to naturally occurring DMAA. The presence of DMAA in the international food supply is sufficient under Section 413(a)(1) because Congress did not limit the geographic scope of the food supply criterion found in that provision. Where Congress wanted

---

[31] *Id.* § 413(d).

[32] *Id.* § 413(a).

to place a geographic limitation in the statute, it did so expressly.[33] As such, DMAA has been present in the food supply and is extracted from geranium without chemical alteration. Thus, DMAA falls under Section 413(a)(1), and not Section 403(a)(2). We are therefore not required to submit an NDI notification to FDA for the DMAA contained in our dietary supplements.

IV. Substantial Data and Analyses Establish A Reasonable Assurance That DMAA Does Not Present A Significant Or Unreasonable Risk Of Illness Or Injury

As FDA recently stated, the DMAA letters were sent only because the recipients of the letters, according to FDA, were required to but "had not submitted NDI notifications for their DMAA supplements."[34] The Roosevelt letter nonetheless states that "To the best of FDA's knowledge, there is no history of use or other evidence of safety establishing that [DMAA] will reasonably be expected to be safe as a dietary ingredient." The letter speculates as to the potential for adverse effects on human health, but references no scientific or medical evidence that DMAA is unsafe or causes harm when consumed in accordance with the labeled Directions for Use and Warnings. The published literature, together with the evaluations conducted by highly respected experts in toxicology and pharmacology, demonstrate the safety of DMAA when used as directed.

Congress's statutory presumption of the safety of dietary ingredients is evident in its explicit pronouncement that "dietary supplements are safe within a broad range of intake, and

---

[33] *E.g.*, FD&C Act Section 413(d) (defining an NDI based on its presence in the United States market prior to October 15, 1994).

[34] Elaine Watson, *AHPA: If DMAA is in geranium, synthesized version is lawful dietary ingredient* (April 30, 2012), *available at* http://www.nutraingredients-usa.com/Regulation/AHPA-If-DMAA-is-in-geranium-synthesized-version-is-a-lawful-dietary-ingredient.

safety problems with the supplements are relatively rare."[35] All dietary supplements and dietary ingredients, new and old, are subject to an adulteration provision prohibiting products that present a "significant or unreasonable risk of illness or injury."[36] For a dietary supplement containing an NDI, there must exist adequate information "to provide a reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury."[37] In the case of DMAA, there is no question that adequate information provides reasonable assurance that DMAA does not present a significant or unreasonable risk of illness or injury.

A. Several Human Studies Support the Safety of DMAA

Seven clinical studies have been conducted to evaluate the safety of DMAA. These studies evaluated the safety of DMAA after single-dose administration and repeat-dose administration over periods of 2, 8, and 10 weeks. Each study has shown that, although DMAA can produce a mild and transient increase in systolic blood pressure, no other safety variables were affected. All seven studies, which are described below and appended to this response, confirm that DMAA is safe when used according to the labeled Directions for Use and Warnings.

- Bloomer et al. (2011a), *Effects of 1,3-Dimethylamylamine and Caffeine Alone or in Combination on Heart Rate and Blood Pressure in Healthy Men and Women*: This study investigated the addition of DMAA and caffeine on resting hemodynamic properties and endogenous sympathetic catecholamine (epinephrine and norepinephrine) levels of volunteers (5 female/5male) for up to 2 hours after dosing. Results: Acute ingestion of DMAA alone and in

[35] Pub. L. No. 103-417, § 2(14).

[36] FD&C Act § 402(f)(1)(A).

[37] FD&C Act § 402(f)(1)(B).

combination with caffeine results in an increase in systolic blood pressure, diastolic blood pressure, and rate pressure product without an increase in heart rate. (Appendix 9.)

- Bloomer et al. (2011b), *Effect of Caffeine and 1,3- Dimethylamylamine on Exercise Performance and Blood Markers of Lipolysis and Oxidative Stress in Trained Men and Women*: Twelve exercise-trained subjects ingested placebo, caffeine, or caffeine plus DMAA 60 minutes before running 10km. Results: A combination of 1mg DMAA/kg and 4mg caffeine/kg, a dose level approximately equivalent to the maximum product label dose, did not significant change physical performance, level of exertion, subject mood or vigor, heart rate, or blood pressure endpoints, compared to placebo, following a very strenuous physical activity. (Appendix 10.)

- Farney et al. (2012), *Hemodynamic and Hematologic Profile of Healthy Adults Ingesting Dietary Supplements Containing 1, 3- Dimethylamylamine and Caffeine*: This study investigated hemodynamic, hematological, and clinical chemistry effects of Jack3d after single and 14-day dosing in seven health adult males. Results: After dosing on days 1 and 14, systolic blood pressure increased (122-12 mm Hg) over pre-ingestion values (109 mm Hg) beginning at 30 minutes. There were not significant differences in acute changes in heart rate, diastolic pressure, or rate pressure product on days 1 or 14, After 14 days of dosing, no significant changes in hemodynamic endpoints compared to day 1 were reported. Fourteen days of dosing did not affect results of blood tests, including complete blood counts and lipid and metabolic panels. (Appendix 11.)

- Farney et al. (2012), *Hemodynamic and Hematologic Profile of Health Adults Ingesting Dietary Supplements Containing 1, 3- Dimethylamylamine and Caffeine*: This study investigated hemodynamic, hematological, and clinical chemistry effects of OxyElite Pro after singe and 14-day dosing in four healthy adult males and two females. Results: After dosing on day 1, systolic blood pressure increased (116-119 mm Hg) over pre-ingestion values (103 mm Hg) beginning at 60 minutes. There were no significant differences in acute change in systolic pressure on day 14, or in heart rate, diastolic pressure, or rate pressure product on days 1 or 14, After 14 days of dosing, no significant changes in hemodynamic endpoints compared to day 1 were report. Fourteen days of dosing did not affect results of blood tests, including complete blood counts and lipid and metabolic panels. (Appendix 11.)

- McCarthy et al. (2012a), *A Finished Dietary Supplement Stimulates Lipolysis and Metabolic Rate in Young Men and Women*: This study examined the effect of a single dose of OxyElite Pro on hemodynamics of healthy adults for up to two hours after treatment. Six males and 6 females were administered

two capsules of OxyElite Pro or placebo on two separate days in a cross-over study design. Results: An increase in heart rate of 8-11 beats/min was reported in the treated group beginning at 60 minutes. Systolic blood pressure increased (112-118 mm Hg) in the treated groups, compared to placebo (101-104 mm Hg) beginning at 30 minutes after dosing. The rate pressure product increased in the treated group at 60 minutes after dosing. There was no increase in diastolic pressure. (Appendix 12.)

- McCarthy et al. (2012b), *Biochemical and Anthropometric Effects of a Weight Loss Dietary Supplement in Health Men and Women*: This study examined the effect of an 8-week exposure of OxyElite Pro on hemodynamic, hematological, and clinical chemistry end points. Groups of 16 health adult males and females consumed 1-2 capsules of OxyElite Pro or two placebo capsules daily for 8 weeks. Results: In the treated group, resting heart was slightly, but statistically significantly, higher (69.4 BPM) at the end of the study compared to the beginning (63.3 BPM), but were not different from placebo control values. There were no differences in systolic or diastolic blood pressure between treatment groups. There were also no clinically relevant differences between treatment groups across time in hematology, lipid, or metabolic panel endpoints. (Appendix 13.)

- Whitehead et al. (2012), *Impact of a Dietary Supplement Containing 1,3-Dimethylamylamine on Blood Pressure and Bloodborne Markers of Health: a 10-week Intervention Study*: This study examined the effect of a 10-week exposure of Jack3d on hemodynamic, hematological, and clinical chemistry endpoints in groups of 12 to 13 healthy adult males. Results: Ten weeks of Jack3d use resulted in reported heart rate and systolic and diastolic blood pressure values similar to placebo controls. There were no clinically relevant differences between treatment groups across time in hematology, lipid, or metabolic panel endpoints. (Appendix 14.)

B. Animal Studies Support the Safety of DMAA

DMAA toxicology has been studied in mice by intraperitoneal and intravenous administration.[38] These data were compared with data in mice for other naturally occurring and commonly consumed compounds (caffeine and phenethylamine). The results of this comparison

[38] Marsh DF, Howard A, Herring DA, *The Comparative Pharmacology of the Isomeric Nitrogen Methyl Substituted Heptylamines*, Journal of Pharmacology and Experimental Therapeutics, volume 103, at 325-329 (November 1951) (Appendix 15).

showed that DMAA has similar toxicity to caffeine (a commonly consumed and safe dietary ingredient) as well as phenethylamine (a constituent of chocolate).[39] In a recently completed toxicology study, the oral LD-50 of DMAA was determined to be approximately 481 mg/kg in rats and 324 mg/kg in rabbits -- showing less than half the toxicity of caffeine, which has an oral LD-50 of approximately 192 mg/kg in rats and 224 mg/kg in rabbits. An oral subchronic 90-day study in rats is scheduled to be completed within the next 60-90 days. Formal reports of both studies will be sent to you as soon as they are available.

C. FDA Has Previously Reviewed the Safety of DMAA as an Active Ingredient in a Drug Under an NDA and Authorized the Marketing of the Product for 30 Years Until It Was Voluntarily Withdrawn by the NDA Holder

On March 22, 1948, Eli Lilly submitted a new drug application (NDA) to FDA for a nonprescription drug, Forthane, with DMAA as the active ingredient. At that time, drug companies were required to submit an NDA demonstrating only that a drug was safe. On April 12, 1948, 39 days before the end of the 60-day statutory period for FDA review, FDA affirmatively authorized Lilly to begin marketing Forthane in the United States as a safe nasal decongestant.[40] Following FDA authorization, Lilly marketed Forthane from 1948 until it

---

[39] Senda S, Hirota K, *Pyrimidine Derivatives and Related Compound. XXII, Synthesis and Pharmacological Properties of 7-deazaxanthine Derivatives*, Chemical and Pharmaceutical Bulletin (Tokyo), volume 22, at 1459-1467 (July 1974) (Appendix 16); Jackson DM, *The Interaction Between Beta-phenethylamine and Agents which Affect the Cholinergic Nervous System on Locomotor Activity and Toxicity in Mice*, Arzneimittelforschung, volume 24, no. 1, at 24-27 (January 1974) (Appendix 17).

[40] FD&C Act Section 201(ff)(3)(B) excludes from the definition of a dietary supplement a product that contains an article that is approved or authorized for investigation as a new drug. Section 201(ff)(3)(B) does not apply to DMAA because DMAA is not approved or authorized for investigation as a new drug.

voluntarily discontinued the product in 1978. DMAA was thus on the market for 30 years. There is no published literature suggesting that Forthane was unsafe. Even after Lilly withdrew Forthane from the market for its own commercial reasons, FDA did not take the technical step of withdrawing approval of the NDA until five years later.

D. An Independent Evaluation of DMAA by Environ Corporation Supports the Safety of DMAA

Environ International Corporation, a leading scientific consulting firm, reviewed all of the available data relevant to the assessment of human health and safety regarding the use of DMAA as a dietary ingredient. The company prepared a safety evaluation[41] authored by, among others, Joseph V. Rodricks, Ph.D., DABT, who is a founder of Environ and an internationally recognized expert in toxicology and risk analysis. Before founding Environ, Dr. Rodricks served as a scientist for FDA for 15 years, where he began as a toxicologist reviewing the safety of food ingredients. During his last four years at FDA, Dr. Rodricks served as Associate Commissioner for Health Affairs. Dr. Rodricks is a member of the Institute of Medicine of the National Academy of Sciences.

The Environ assessment concludes that "there is no scientific evidence that the labeled use of [DMAA products] by healthy adults will compromise individual health or increase susceptibility to heat-related injuries." In developing the safety assessment, Environ reviewed the following data: a literature search performed by Environ of the PubMed database and ToxNex search engine for published studies of DMAA (and chemical nomenclature synonyms),

[41] Joseph V. Rodricks et al., *Safety Evaluation of 1,3-Dimethylamylamine (DMAA) in Dietary Supplement Products* (May 2012) (Appendix 18).

and our dietary supplements containing DMAA; six publications (seven studies total) of human clinical studies of DMAA in healthy men and women; four studies in animals and humans published from 1927 to 1953; the U.S. patent for aminoalkanes; a safety assessment of DMAA performed by Cantox Health Sciences International; and FDA adverse event reports on dietary supplements. The Environ Report concludes that:

> hemodynamic effects (heart rate and blood pressure), or lack thereof, were similar across the studies regardless of whether subjects ingested DMAA, caffeine, DMAA and caffeine, [or our DMAA-containing dietary supplements].

Specifically, the Environ Report concluded that the blood pressure changes associated with DMAA and caffeine "are offset by reduced heart rate (4-5 bpm) to maintain consistent cardiovascular load."

Environ was unable to find any scientific or medical evidence that DMAA is unsafe when used according to the labeled Directions for Use and Warnings. Environ's exhaustive review of all of these materials and its conclusion that DMAA is a safe dietary ingredient provides strong support for determining that DMAA does not present a significant or unreasonable risk of illness or injury when taken as directed.

E. An Independent Evaluation of DMAA by Cantox Health Sciences Corporation Supports the Safety of DMAA

Cantox, another leading scientific consulting firm, also undertook an independent safety review of DMAA.[42] Cantox's conclusions are the same as those detailed in the Environ

[42] Intertek Health Sciences International, *supra* n. 5.

assessment: Used as directed, "it is unlikely that DMAA consumption from these products would cause adverse effects when used . . . by the appropriate population." The Cantox Report evaluated the publicly available data on DMAA, which included metabolic data, pharmacological data, animal data, and human clinical studies.

F. The Stimulant Effect of DMAA When Used as Directed is Comparable to the Stimulant Effect of 2 to 3 Cups of Coffee

The safety of DMAA as a dietary ingredient is further supported by the fact that the stimulatory hemodynamic effects, including short term increases in blood pressure, when used as directed, are statistically identical to those from the amount of caffeine in 2 to 3 cups of coffee.[43] Environ has documented the comparable effects of caffeine and DMAA in the attached analysis.[44] As Environ concludes, "caffeine and DMAA have both exhibited very good tolerance by adults," and the clinical trials using the combination of both substances "do not indicate that consumption of both compounds…would increase the susceptibility of adults to adverse cardiovascular events while exercising."

G. The Adverse Event Reports Received by FDA and the Company for DMAA Do Not Reveal a Single Serious Adverse Event Resulting from use in Accordance with the Labeled Directions for Use and Warnings

We have a robust system in place to receive and analyze consumer complaints and adverse event reports alleged to be associated with our products. Analyses of all such data and information we received as of the date of the Roosevelt letter reveals not one serious adverse

[43] Joseph V. Rodricks, *supra* note 33, at 9.

[44] Environ International Corporation, *A Comparison of the Physiological Effects of Caffeine and Dimethylamylamine (DMAA)* (May 8, 2012) (Appendix 19).

event report associated with the use of the company's products under the conditions of use recommended or suggested in the labeling.

1. Mandatory Adverse Event Reports Made by Us

As a preliminary matter, we emphasize that both the governing law[45] and FDA guidance[46] make clear that the submission of a serious adverse event report to the agency is not an admission that the dietary supplement involved caused or contributed to the adverse event being reported. The manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all reports it receives alleging that a serious adverse event was associated with the use of a dietary supplement product, whether or not the alleged events are in fact causally related to its product.[47] Thus, in accordance with the law, upon receiving three reports alleging serious adverse events, we forwarded those reports to FDA. We do not believe, however, that any of the three incidents are evidence of a genuine safety issue associated with the product.

First, in all three cases, the consumers failed to use the product as labeled in the Directions for Use, failed to follow the label Warnings, or both. For example, a mandatory report submitted in March 2010 involved the use by a 16-year-old of a product with a black box warning prominently displayed on the principal display panel and other warnings repeated in dosing instructions stating that the product is not for use by individuals 18 years or younger.

---

[45] FD&C Act § 761(g).

[46] FDA/CFSAN, *Guidance for Industry: Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act* (Revised June 2009).

[47] FD&C Act § 761(b).

other stimulants or combined with other products containing caffeine.

More importantly, it is unclear that the ingestion of the product played a role in any of the three incidents. Indeed, in one of the three incidents, the person reporting the incident "believed" the subject had been taking the product for a period of time prior to the incident, but could not confirm whether the subject had consumed the product prior to the incident and did not state that the product played a role in the events that transpired. In another incident, the subject was performing exercise in extreme heat. In another, the consumer was taking a powerful prescription medicine that has been associated with sudden cardiac death and cardiac arrhythmia. The subject was also obese, based on his reported body weight and height. These reports do not provide data or information to suggest that DMAA was responsible for the incidents.

More fundamentally, and as discussed more fully above, the safety of DMAA has been well documented in seven clinical studies, none of which involved any serious adverse events and none of which demonstrated any statistically significant effect of the product upon cardiovascular risk factors such as those alleged to be linked to the product in two of the serious adverse event reports. As such, we do not believe that any of the mandatory adverse event reports submitted to FDA constitute evidence of a genuine safety issue caused by the product.

Finally, it has been brought to our attention that a serious adverse event report was made to FDA by another dietary supplement company, Iovate, regarding an incident that involved the ingestion of the same product in addition to numerous other supplements. However, the incident did not meet the statutory definition of a "serious adverse event," in

Section 761(a)(2) of the FD&C Act. A serious adverse event is defined as one that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.[48] The subject of the Iovate report claimed to have experienced chest pain and heart fluttering, but did not seek a medical evaluation and was not admitted to the hospital. The incident therefore did not constitute a serious adverse event as defined by the statute. In addition, the consumer took the product in clear violation of the labeled Directions for Use and Warnings. He consumed it while taking other supplements and while consuming caffeine. In light of these facts, the report submitted by Iovate does not suggest that DMAA poses a safety issue when used in accordance with its labeled conditions of use.

2. Voluntary Adverse Event Reports Made By Other Parties

As of the date we received the Roosevelt letter, we were aware of 21 voluntary adverse event reports filed with FDA regarding events allegedly associated with the use of DMAA. These 21 reports were made between the years 2009 and 2012, during which time an estimated one billion servings of dietary supplements containing DMAA were sold by the dietary supplement industry in the United States. These reports do not support a causal relationship of DMAA with serious health risks for a number of reasons.

First, 12 of the 21 reports involved use of the product in violation of its labeled Directions for Use and Warnings, including dosages greater or more frequent than those in the

[48] FD&C Act § 761(a)(2). In addition, a serious adverse event could be one that required, based on reasonable medical judgment, a medical or surgical intervention to prevent the aforementioned serious outcomes.

labeled dosage instructions and uses in conjunction with other supplements, stimulants, and medications.

Second, at least nine of these incidents did not meet the statutory definition of a "serious adverse event." As noted above, a "serious adverse event" is defined in Section 761(a)(2) of the FD&C Act as one that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.[49] A number of the voluntary reports alleged reactions falling far below that standard, including allegations of acne breakouts, tongue numbness, and pupil dilation.

Finally, the information included in these voluntary reports do not establish a causal relationship with the use of our products. A number of the voluntary reports variously included no information as to duration of use or dosage of our product, age of the consumer involved, or any relevant diagnostic values. More significantly, as discussed above, clinical trials demonstrate no adverse events or statistically significant alterations in cardiac function or blood pressure from the administration of DMAA. As such, the voluntary adverse event reports demonstrate no evidence of genuine safety concerns associated with our DMAA products.

V. Conclusion

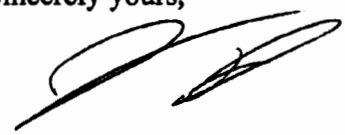
For the reasons set forth in this letter, DMAA is a lawful dietary ingredient that is used in compliance with the requirements of the FD&C Act, as amended by DSHEA.

[49] FD&C Act § 761(a)(2).

VI. Confidentiality

The information in this submission constitutes trade secrets and confidential information that is exempt from public disclosure under 5 U.S.C. § 522. FDA is prohibited from disclosing this information pursuant to 18 U.S.C. § 1905 and Section 301(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331(j).

Sincerely yours,



Jonathan V. Doyle
President